

Application No. 09/543,679
Supplemental Amendment dated June 14, 2004
Reply to Office Action of February 11, 2004

THE REMARKS

Claims 92-125 are pending in the application.

Preliminary Remarks

This Supplemental Response is being submitted to supplement the Response to Office Action, mailed April 13, 2004 in response to the Office Action dated February 11, 2004, as well as a telephone interview with Examiner Janet Epps-Ford on May 20, 2004. In the telephone interview, Examiner Ford acknowledged that:

- The pending claims are free of the prior art in view of the arguments filed in the Amendment and Response of April 13, 2004;
- The Bradykinin B2 receptor experiments disclosed in the Robinson Declaration was convincing in support of the pending claims;
- The Eotaxin experiments were not convincing because the structure of the antisense oligonucleotides was not disclosed. Applicant acknowledges that the Declaration by Dr. Cynthia B. Robinson, M.D., omitted the Eotaxin nucleic acid sequences needed to fully appreciate the importance of the disclosed examples within the Declaration. Applicant provides the Eotaxin nucleic acid sequences in this Response below;
- The IL4-R α and IL9-R α experiments were not applicable in the instant application because the disclosed antisense oligonucleotides were outside the scope of the claims. Applicant acknowledges that the IL4-R α and IL9-R α examples were outside the scope of the claims in regards to the adenosine content of the antisense oligonucleotides. Applicant, however, respectfully points out that the IL4-R α and IL9-R α examples are applicable to the instant claims in regards to the small particle size of the example, and therefore submit that the example should be considered in that context.

Applicant requests that the Examiner reconsider the application in light of the remarks contained herein.

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35 U.S.C. § 112, 1st paragraph Rejection Written Description

The Examiner rejected Claims 92-125 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In addition, the Examiner objects to Claim 92 as lacking a direct relationship between the recited terms "target polynucleotide" and "antisense oligonucleotide."

Applicant acknowledges the Examiner's comment regarding the lack of a "direct relationship between the 'target polynucleotide' (line 2) recited in claim 92, and the 'antisense oligonucleotide' (see line 4) recited in claim 92." Applicant has amended the claim to read "An in vivo method of delivering a pharmaceutical composition to a target polynucleotide comprising administering to the airways of a subject said pharmaceutical composition of a respirable or inhalable particle size of 0.5 um to 10 um in size or 10 um to 500 um in size comprising at least one antisense oligonucleotide to said target polynucleotide effective to alleviate hyper-responsiveness to adenosine ..." The amendment is supported in the specification, for example, by page 2, lines 35-40, and does not add new matter. Applicant respectfully requests that the objection be withdrawn.

Applicant respectfully traverses the Examiner's contention regarding the alleged lack of written description. The written description requirement under 35 U.S.C. § 112 carries with it a "strong presumption that an adequate written description of the claimed invention is present when the application is filed." See 66 Fed. Reg. 1104 ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement"), citing *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976). The burden, therefore, rests with the U.S. Patent and Trademark Office to show that the specification does not meet the written description requirement. Applicant respectfully contends that the Examiner has failed to meet her burden.

To satisfy the requirements of 35 U.S.C. § 112, an applicant may describe "distinguishing, identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." 66 Fed. Reg. 1105. An applicant may show adequate written description by providing a "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1106. In addition, it is important to note that an

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applicant need not disclose "[w]hat is conventional or well known to one of ordinary skill in the art . . . in detail." *Id.* More explicitly, "[i]f a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." *Id.*

The Examiner respectfully has not met her burden in showing that the instant application does not meet the written description requirement. The Applicant has provided adequate support and evidence in the specification to support his claim. Specifically, the Applicant has disclosed that an adequate and representative number of antisense sequences are operable, and supported this finding with a broad disclosure as to the applicability of the claims. More importantly, the Examiner has not shown any evidence that the claimed invention does not work, nor any reason why one skilled in the art would question that the disclosed invention would not work as claimed. The Examiner contends that "further experimentation would be required to identify an antisense oligonucleotide that would be effective [in the present invention]." The Examiner is incorrect. The necessity for "further experimentation" is not the standard for the written description requirement. It is only necessary that one of ordinary skill in the art would have understood the inventor, as provided by the written description, to be in possession of the claimed invention at the time of filing.

Applicant has provided sufficient disclosure in the specification to convey to one of ordinary skill in the art that Applicant was in possession of the instant invention.

Applicant respectfully points out to the Examiner that the instant application already discloses a successful example of an *in vivo* application of the instant invention. Applicant also points to supporting examples of the instant invention in the Declaration from Dr. Cynthia B. Robinson, M.D. In her Declaration, Dr. Robinson describes three additional *in vivo* examples other than an adenosine receptor for the use of antisense oligonucleotides in the treatment of asthma and pulmonary diseases. Specifically, Dr. Robinson describes the successful use *in vivo* of antisense oligonucleotides against bradykinin B2, eotaxin1 and IL4-R α and IL9-R α . The examples use the teachings of the invention, particularly that the oligonucleotides contain no more than 3 adenosines if at least 21 nucleotides

¹ The declaration lacks the sequence information for eotaxin. The sequence of AS-18 and AS-18MM in the example is 5' - TTG GTC CAG GTG CTT TGT GG - 3' and 5' - TTG GCT CAG GTG CTT GTT GG - 3', respectively. Applicant apologizes for this omission.

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long, and has a particle size of about 0.5 μm to about 10 μm , or 10 μm to about 500 μm . These examples, using the novel particle size composition of the instant invention, show that, contrary to the Examiner's contentions, in vivo applications using the teachings of the instant invention is successful, and not unpredictable as contended to by the Examiner. The instant invention is sufficiently disclosed.

As support that the specification contains sufficient disclosure, Applicant directs the Examiner to the differences between the disclosure in the instant application and the factual situations in the precedential DNA cases of 35 U.S.C. § 112, 1st paragraph, namely *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) and *U.C. Regents v. Eli-Lilly*, 119 F.3d 1559 (Fed. Cir. 1997), as well as the U.S. Patent and Trademark Guidelines on Written Description (*see* 66 Fed. Reg. 1104). In *Fiers*, the court held that "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Fiers*, 984 F.2d at 1170. Specifically, the court in *Fiers* found that the claim was not supported by the specification because the specification did not provide sufficient support as to how one of ordinary skill in the art could obtain the claimed DNA. Similarly, in *Eli-Lilly*, Appellants failed to meet the written description requirement because the specification supported only rat cDNA, not human cDNA, and only provided amino acid sequence information for human insulin A and B chains. *Eli-Lilly*, 119 F.3d at 1567.

In contrast, at the time of filing of the instant application, one of ordinary skill in the art already had access to a large number of nucleic acid sequences applicable to the instant invention because they were already cloned and sequenced and were already available to a skilled practitioner either in the specification or through public databases. Therefore, unlike the scenario in *Fiers* or *Eli-Lilly*, one of ordinary skill in the art already had access to the nucleic acid sequences of the claimed invention, providing sufficient structural information to a practitioner in the art. The situation in the instant application is more akin to *Enzo Biochemical v. Gen-Probe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002), where the court clarified *Eli-Lilly* and held that the written description requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. *Id.* at 1324. In the instant application, a large number of the nucleic acid sequences are clearly known and available, either through the specification or public databases,

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to those of ordinary skill in the art, making the disclosed function of the instant claims sufficiently correlated to a particular known structure.

Moreover, as the Examiner has noted in the Office Action mailed February 11, 2004, the claimed invention contains additional structural descriptions as limitations, specifically the length of the antisense oligonucleotide, the oligonucleotide composition of 15% or less adenosine, as well as in the amendments of April 13, 2004, adding the limitations that the oligonucleotide is antisense to the initiation codon, the coding region of the 5' and 3' intron-exon junctions of a gene or mRNA encoding a protein associated with hyper-responsiveness to said disorders. These limitations show adequate written description by providing a "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." 66 Fed. Reg. 1106. These limitations, combined with the adequate and sufficient disclosure of examples in the specification, form the "common attributes or characteristics that identify the members of the claimed genus." Office Action at 7. Because the disclosure provides adequate and sufficient disclosure to describe the claimed genus, the specification meets the written description requirement.

The Examiner points to Krieg et al. (U.S. Patent No. 6,207,646), which the Examiner alleges that it teaches that the limitation in the instant application of oligonucleotides comprising less than 15% adenosine in vivo is insufficient to design an effective antisense oligonucleotide that is capable of alleviating bronchoconstriction, asthma, or lung allergy. Office Action at 6. Applicant respectfully disagrees that the Krieg et al. patent is applicable to the instant invention, and again reiterates that the Krieg et al. patent lies outside of the scope of the invention. In addition, Applicant points out that the experiment disclosed within the Krieg et al. patent is not against the claims to the instant invention as contended by the Examiner.

Firstly, Applicant respectfully points out that the Krieg patent is not applicable to the instant invention because it is outside the scope of the claims. The Krieg patent describes heretofore uses of oligonucleotides in vivo, specifically uses whereby oligonucleotides are injected intraperitoneally, rather than the direct targeting mechanism in a tissue-specific manner disclosed in the instant invention. See '646 patent, col. 42, lines 19-27. Direct targeting of the invention through small particle aerosolized distribution avoids the many problems inherent in delivering oligonucleotide

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compositions, one of which is the degradation, dilution and transport of the oligonucleotides to the target cell where it is needed. The Krieg patent is therefore not applicable to the instant invention, because it does not utilize the limitation of the instant invention of the use of a direct targeting system. The Krieg patent lies outside of the scope of the claims.

Similarly, the Krieg patent goes outside of the claims because it does not address the effects of oligonucleotides antisense to a target protein to alleviate bronchoconstriction, asthma or lung allergy. The Examiner contends that the 15% adenosine oligonucleotide disclosed in the Krieg patent to prevent the development of an inflammatory condition associated with asthma in mice. The Examiner contends that the "limitations describing the percent adenosine in the antisense oligonucleotide and its length are insufficient to design an effective antisense oligonucleotide that is capable to alleviate bronchoconstriction, asthma, or lung allergy." Office Action at 6. First, the Examiner is incorrect in asserting that identical oligonucleotides were used in the experiment. On the contrary, an unmethylated CpG oligonucleotide, TCCATGACGTTTCCTGACGTT (CpG methylation sites underlined) and a control oligonucleotide, TCCATGAGCTTCCTGAGTCT (methylation sites removed) were used, not identical sequences as postulated by the Examiner. Therefore, even though the two oligonucleotides have the same identical adenosine content, the experiment does not show that "percent adenosine in the antisense oligonucleotide are insufficient to design an effective antisense oligonucleotide" because the experiment uses a control mismatched oligonucleotide that is incapable of binding to a target.

Moreover, the experiments disclosed in the Krieg patent do not utilize antisense oligonucleotides. Instead, the premise of the Krieg patent is to look at the effects of non-specific, non-binding CpG unmethylated oligonucleotides as an immunostimulator. See '646 patent, col 13, line 47 to col. 14, line 12, discussing mismatch control antisense oligonucleotides having a stimulatory effect. As further support, a database search with the Krieg oligonucleotides described above found that the Krieg oligonucleotides were not antisense oligonucleotides to either IL-4 or IL-5 described in the Krieg application. Compare Accession Nos. NM_010558 (mouse IL-5 cDNA) and NM_021283 (mouse IL-4 cDNA) with Krieg oligonucleotides. The Krieg oligonucleotides were not utilized as antisense oligonucleotides, and therefore lie outside of the scope of the claims.

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For these reasons, the experiment disclosed within the Krieg patent does not go against the findings of the instant invention. The Krieg patent is not applicable to the instant application, and lies clearly outside the scope of the claims of the instant invention.

The Examiner points to the numerous structural variants of the gene and mRNA targets claimed in the instant invention as additional support that the applicant could not have possession of the instant invention at the time of filing. The Examiner's contention is wrong. That one of ordinary skill in the art has access to the claimed sequences of the instant invention applies equally to structural variants of the claimed invention, such as alleles or polymorphisms of the gene and mRNA targets, as the variants are identified through substantial homology or structural similarity to the already published and well-known sequences. The specification provides more than sufficient detail regarding the teachings of the invention.

The Examiner also contends that the claimed invention is not adequately described because it is described in terms of its function. The Examiner is incorrect, for the above reasons, in stating that the invention is solely described by a functional characteristic. Because the claimed invention provides for known sequence structure information, as well as provides further limitations regarding the structure of the oligonucleotides, the claimed invention is not described solely in terms of a functional characteristic. The combination of sufficient structural information provided by the knowledge of one of ordinary skill in the art, as well as the claim itself, meets the written description requirement.

For the foregoing reasons, Applicant submits that the instant invention was described in the specification to reasonably convey to one skilled in the relevant art that he had possession of the claimed invention. The Examiner is respectfully requested to withdraw this rejection.

In summary, applicant contends that the written description for the claimed inventions is present and meets 66 Fed. Reg. 1104 ("Guidelines for Examination of Patent Applications under 35 U.S.C. 112 ¶1), and recent case law. These Guidelines were enacted January 5, 2001. Subsequent to enactment of these guidelines, claims in the parent application, substantially identical to the instant claims, were allowed four (4) separate times. As noted above, even taking those Guidelines in account, and the recent case law, the instant claims and written description are distinguishable from those instances where the Guidelines were intended to apply.

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Therefore, consistent with the four (4) separate office actions allowing the claims in the parent application, the instant claims should be found in full compliance with 35 U.S.C. § 112, ¶ 1, and allowed.

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CONCLUSION

In view of the foregoing amendment and remarks, the Applicant believes that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 565-3585.

Respectfully submitted,

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